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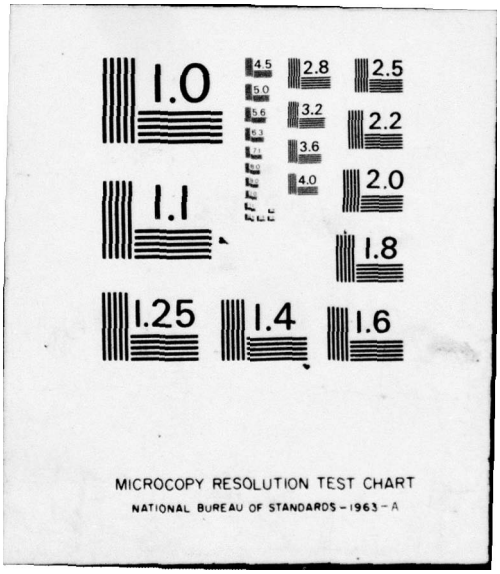
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Research Report CCS 269

STATISTICAL ESTIMATION OF THE PHARMACOKINETIC PARAMETERS IN THE ONE COMPARTMENT OPEN MODEL

by

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July 1976

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SUMMARY

A comparative blood-level trial is undertaken to evaluate the in vivo performance of drug formulations in human subjects. A known amount of drug is administered and plasma levels are measured at specified times. The resulting concentration-time curve reflects the absorption, distribution and elimination of the drug. The simplest model that represents this kind of data is the one compartment open model. In many situations this serves as a convenient model for estimating the bioavailability parameters--area under the concentration-time curve, time to peak concentration, and peak concentration.

The one compartment open model is nonlinear in the unknown parameters and is usually fit using least squares. Gradient methods often fail for real world data, and we have found the Nelder-Mead simplex algorithm provides a useful alternative. Further, we propose that least absolute deviation criteria be used as a robust alternative to least squares. Both least absolute deviation and least squares estimates can be obtained using an iterative weighted least squares algorithm. The iterative weighted least squares procedure is also used to obtain maximum quasi-likelihood estimates and robust estimates using the sine weight function. Two numerical examples are presented.

1. INTRODUCTION

Pharmacokinetics is the study of the rate processes involving absorption, distribution, metabolism and excretion of drugs in the intact total organism. Generally, pharmacokinetic data are generated by administering a dose of a drug to the subject(s) and measuring drug and/or metabbolite levels as a function of time. Sampling is usually limited to a few easily accessible areas of the body such as blood, urine and feces. These data are then often evaluated utilizing linear compartmental models to describe the drug and metabolite levels in the body as a function of time. The model chosen to describe the "body" is the simplest compartmental system consistent with the observed data and some semblance of physiological reality.

Conceptual problems encountered in the application of compartmental theory to biological systems have been discussed in the symposium proceeding edited by Bergner and Lushbaugh (1967). When the transfer rates between compartments are constant, the system is represented as a system of first-order linear differential equations with constant coeficients. An excellent review of the mathematical problems of compartmental analysis and applications of the general theory to physiological systems has been provided by Rubinow and Waryer (1971). They emphasize the importance of establishing appropriate constraints on the parameters in the model if a unique mathematical representation is to be achieved.

In addition to the conceptual and mathematical problems that must be resolved in developing a compartmental model, the problems of data analysis must also be considered. Drug concentrations are measured and the pharmacokinetic parameters are then estimated using least squares. The

scientist must know in which compartment(s) (and at what times) measurements should be made to provide data that will allow estimation of the unknown parameters. Shah (1976) has shown that if a drug is introduced into the first compartment of k-linearly connected compartments and elimination occurs from the last compartment (where drug concentrations are measured), then the first order rate constants are not uniquely estimable if there are more than two compartments.

In this paper we shall consider the application of pharmacokinetics in humans as it pertains to an area of medical therapeutics known as bioavailability. Bioavailability includes the study of the factors which influence and affect the processes by which an administered dose reaches the site of pharmacologic action. It is usually defined in terms of the rate and extent to which the drug is delivered from the dosage form into the body. Metzler (1974) has discussed the medical, pharmacological and statistical questions that should be considered in the scientific assessment of the bioavailability in humans. The one-compartment open model (see Exhibit 1) will be used to describe the temporal fate of plasma concentration. This is the simplest of realistic compartment models that can be used to describe the concentration-time data that is obtained in bioavailability studies. The model - see (1) - is nonlinear in the unknown parameters, and is usually fit using least squares (LS). We propose a new robust method of estimation using the least absolute values (LAV) criteria. Both LS and LAV estimates can be obtained using the Nelder-Mead simplex algorithm or via an iterative weighted least squares (IWLS) procedure. Limitations of both approaches are considered and a combined algorithm is proposed for routine data analysis. The combined

algorithm is then extended by adopting different definitions of the weights in the IWLS algorithm. A second robust estimation procedure is developed using the sine weight function. We then show in Section 5 how maximum quasi-likelihood estimates can be obtained using the IWLS algorithm. Two numerical examples are presented.

2. ONE COMPARTMENT OPEN MODEL

A multicompartment system is linear if the exchange of drug is between adjacent compartments according to first-order rate constants, and is open if drug is eliminated from one of the compartments - see Shah (1976). If a known amount of drug (D) is administered orally and is then absorbed into the blood from which elimination occurs, then we have the simplest possible open compartment model (see Exhibit 1). If y_i is the observed serum concentration at time x_i, then the expected concentration is given by

$$f(x_i, \underset{\sim}{\alpha}) = \frac{\alpha_3 \alpha_1}{(\alpha_1 - \alpha_2)} \left[\exp(-\alpha_2 t_i) - \exp(-\alpha_1 t_i) \right] \qquad (1)$$

where $t_i = x_i - \alpha_4$, $i = 1,\ldots,n$, and $\alpha_3 = fD/V$. Here V is the apparent volume of distribution, f is the fraction of drug ultimately absorbed into the blood, α_1 is the absorption rate constant, α_2 the elimination rate constant, α_4 is a delay time.

Rodda, Sampson and Smith (1975) have considered estimation for this model when $\alpha_4 = 0$. In many situations a "better" fit will be obtained with the addition of this time shift parameter. Further, we require that all parameters are positive and that α_1 is greater than α_2. This inequality constraint is based on assumptions about the pharmacokinetic properties of the drug under study. Without this constraint a second best fit can be obtained by interchanging the estimates of α_1 and α_2 and letting $\alpha_3' = \alpha_3\alpha_2/\alpha_1$. The existence of two minima of the sum of squares function is shown graphically in Exhibits 2, 3 and 4. These plots show a three dimensional perspective representation of the sum of squares surface

(with overlaid contours) for the concentration-time data in Exhibit 8. The one compartment open model (1) with $\alpha_4 = 0$ was used in (2) - with p = 2 - and the value of α_3 was fixed at the LS estimate. If a particular sum of squares value exceeded the sum of squares about the mean it was replaced with this constant value, i.e. with $\Sigma_i(y_i-\bar{y})^2$. In Exhibit 2 the "view point" is directly above the diagonal line $\alpha_1 = \alpha_2$ at the point of intersection with a line connecting the two optimal solutions. This corresponds to $\Phi = 8.1^o$, $\Theta = 45$, and D = 4.5, where Eulers angles Φ and Θ define the elevation above the perspective plane and rotation about the S axis, respectively. D is the distance from the view point to the origin in the perspective plane. The plots were generated using a Fortran program PERSPEC -- see Phillips (1971). The view point in Exhibit 3 is directly above the LS estimates $\hat{\alpha}_1 = .656$ and $\hat{\alpha}_2 = .234$ (see Exhibit 9). In Exhibit 4 the view point is above $\alpha_2 = .234$ looking back to the origin at a 45^o angle (D = 4.5, $\Phi = 45^o$, $\Theta = 4.22^o$). It is not difficult to visualize the problems that can occur with gradient type search procedures if the LS estimates are near the boundary $\alpha_1 = \alpha_2$. If the inequality constraint $\alpha_1 > \alpha_2$ is not part of the search procedure the alternate solution can be obtained, or $\alpha_1 - \alpha_2$ may be less than the precision of the computer being used. This is one of the sources of numerical problems that occur with gradient type search procedures used to obtain LS estimates.

At this point we emphasize that in a comparative bioavailability study the pharmacokinetic model (1) will be used to describe serum concentration in a number of different subjects. The objective is to infer therapeutic equivalence of two (or more) formulations of the same chemical

entity without doing efficacy trials. The basic bioavailability assumption is that two formulations that do not differ very much in the rate and extent to which they make the active ingredient available in the circulating blood will not differ much in their therapeutic efficacy. In many comparative bioavailability studies different subjects will receive two (or more) formulations, concentration-time curve data are obtained, and the parameters in (1) are then estimated. Two design questions arise: (i) at what time points should the concentrations be measured, (ii) how should the subject formulation combinations be arranged. Bioavailability is then assessed by comparing the estimated pharmacokinetic parameters or other characteristics of (1). The most frequently used bioavailability parameters are the area under the plasma or blood level versus time curve (AUC), time to peak concentration t^*, and the maximum concentration y^*. These bioavailability parameters are functions of the pharmacokinetic parameters

$$AUC = \int_0^\infty f(x,\underset{\sim}{\alpha})dx = \alpha_3/\alpha_2 \quad ,$$

$$t^* = \alpha_4 + \frac{\ln(\alpha_1/\alpha_2)}{(\alpha_1-\alpha_2)} \quad , \text{ and}$$

$$y^* = f(t^*,\underset{\sim}{\alpha}) \ .$$

Clearly, these parameters are dependent upon the correctness of the model (1). In the rest of this paper we assume that this is a reasonable model and consider the statistical estimation problem. The extrastatistical questions and other statistical approaches to the problem have been discussed in detail by Metzler (1974). There are two major factors that

will be considered. First, what type of sampling distribution seems appropriate for the concentration data. This will be affected by both the variation inherent in the assay and physiological variation. A second question of considerable practical importance is the robustness of the estimation procedure to one or more stray data values.

3. ESTIMATION BY MINIMIZATION

The most widely used approach to developing an estimation procedure assumes that the concentrations are observed values of random variables composed of a constant part given by the regression function (1) and an unobservable error

$$y_i = f(x_i,\underset{\sim}{\alpha}) + \varepsilon_i \ , \quad i = 1,\ldots,n,$$

where the ε_i's have zero expectation, constant variance, and are independent. Then, given the observed y_i's estimates of $\underset{\sim}{\alpha} = (\alpha_1,\alpha_2,\alpha_3,\alpha_4)'$ are obtained by minimizing

$$\sum_{i=1}^{n} |y_i - f(x_i,\underset{\sim}{\alpha})|^p \ , \qquad (2)$$

where $p \geq 1$. In particular, when $p = 2$ we have the least squares procedure, and since $f(x,\underset{\sim}{\alpha})$ is nonlinear in the parameters an iterative algorithm is required (see section 4).

It is generally recognized that while least squares is a good method under ideal conditions, the occurrence of stray values (i.e. outliers) may have devastating effects. This is true for regression functions that are linear in the parameters - see e.g. Andrews (1974), Beaton and Tukey (1975) who have developed techniques for obtaining estimates that are resistant to the effect of stray values using iterative weighted least squares.

The effect of outliers on LS estimates in the one-compartment open model has been considered by Rodda, Sampson and Smith (1975). They developed an ordered simultaneous estimation procedure (OSEP) for the

model (1) with $\alpha_4 = 0$. Their procedure requires partitioning of the data into three regions corresponding to an absorption phase, peak and distributional phase. Selecting points from each of the three regions generates a system of three (nonlinear) equations with three unknown parameters (our α_1, α_2 and α_3). These equations are solved and the procedure is repeated for all possible triples. The OSEP estimate of each parameter is then obtained by determining the median of the parameter values obtained from all possible sets of three points.

Another approach that will produce robust estimates is to set p = 1 in equation (2), i.e.

$$\underset{\underset{\sim}{\alpha}}{\text{minimize}} \quad \Sigma_i |y_i - f(x_i, \underset{\sim}{\alpha})| \quad . \tag{3}$$

When the regression function $f(x_i, \underset{\sim}{\alpha})$ is linear in the parameters, LAV estimates can be obtained using linear programming or via IWLS (see section 5). Armstrong and Frome (1976) have compared these two approaches for the linear regression case, and the linear programming approach is by far superior. The linear programming approach to LAV estimation does not readily extend to the nonlinear case. The IWLS approach to LAV estimation can be extended to the present situation, or any nonlinear regression problem (as has been suggested by Schlosmaker [1974]).

Another approach to minimizing (2) with p = 1 (LAV) or p = 2 (LS) is the Nelder-Mead (1965) simplex procedure. This is a direct search procedure that does not require derivatives and which is easily adapted to incorporate inequality constraints. This algorithm has been coded in ANSI standard FORTRAN subroutine NELMIN by O'Neil (1971). Chambers and Ertel (1974) have made several corrections and suggested some improvements

in NELMIN. Olsson and Nelson (1975) have discussed the use of NELMIN in solving nonlinear LS and several other statistical problems that require function minimization.

The subroutine NELMIN can be used to solve the LAV or LSQ problem with the FORTRAN function shown in Exhibit 5. NELMIN also requires user supplied values to initiate the procedure, define the step size, and determine when convergence has occurred (or terminate the procedure).

To illustrate the use of NELMIN as well as the robustness of the LAV estimates we use the data shown in Exhibit 6. Rodda, Sampson and Smith used this data to compare OSEP and LS when a single outlier is present at different points in a typical plasma concentration-time curve. Note that we have modified their data to produce patterns with one, two and three outliers. Further, we have included Pattern 7 with an outlier in the elimination phase of the curve, and we have expressed time in hours rather than minutes. The "true" parameter values are $\alpha_1 = 3.0$, $\alpha_2 = 0.3$ and $\alpha_3 = 50$.

The following procedure was followed in obtaining the results shown in Exhibit 4:

1. Set $\alpha_1 = 25$, $\alpha_2 = 1$, $\alpha_3 = 10$, and set the step size for each parameter equal to one tenth of the parameter value. These are the values for START and STEP. The values for KONGUE and ICOUNT were set equal to 25 and 7777, respectively, and REQMIN = 10^{-12}.
2. Use subroutine NELMIN to obtain LS estimates, i.e. set LP = 2 and call NELMIN.
3. Set LP = 1 and with the LS estimates as starting values use NELMIN to obtain LAV estimates of the parameters.

4. Repeat step 2 using the LAV estimates as starting values. This provides a check on the results in step 2.

The LS and LAV estimates of the pharmacokinetic parameters (i.e. the α's) are then used to calculate estimates of the bioavailability parameters (see Exhibit 7). This same program has been used to obtain estimates of the bioavailability parameters in several comparative bioavailability studies. It has been our experience that the algorithm NELMIN achieves the same minimum value and converges to the same optimal solution for LS problems, provided the difference between α_1 and α_2 is small. When α_1 and α_2 are almost equal alternate optimal solutions with the same minimum value for the objective function can be obtained. This indicates that the appropriate model to consider is the equal roots solution of the original differential equations, i.e. the expected concentration at time x is

$$\alpha_1\alpha_3(x - \alpha_4)e^{-\alpha_1(x - \alpha_4)} \quad . \tag{4}$$

This is an interesting situation since $\alpha_1 = \alpha_2$ in Exhibit 1 yields equation (4) for the concentration-time curve. The restricted model (4) is not a special case of (1), and conceptually there are still two parameters - the absorption rate constant and the elimination rate constant. Yet, from an estimation point of view there is one less parameter, i.e. we have one less degree of freedom in the parameter space.

Here we see one of the advantages of the Nelder-Mead procedures where the inequality constraint $(\alpha_1 - \alpha_2) > 0$ is easily imposed. In practice this is implemented by assigning the objective function a large value if $(\alpha_1 - \alpha_2) \leq \varepsilon$, where ε is a small positive number. If the algorithm terminates with $\alpha_1 - \alpha_2$ almost equal to ε then we are near a

boundary of the parameter space, and the estimation procedure should proceed using (4) rather than (1) as the appropriate model. The main disadvantages of the Nelder-Mead procedure are that (i) it may not be efficient, (ii) it does not provide estimates of the standard errors of the parameters. These difficulties can be overcome by combining NELMIN with the IWLS procedure described in the next section.

4. ESTIMATION USING IWLS

Consider the following weighted sum of squares - which is to be minimized with respect to $\underset{\sim}{\alpha}$ -

$$\sum_{i=1}^{n} w_i [y_i - f(x_i, \underset{\sim}{\alpha})]^2 , \tag{5}$$

where w_i's are nonnegative "weights". Since $f(x, \underset{\sim}{\alpha})$ is nonlinear in the parameters we expand it about an initial estimate, $\underset{\sim}{\alpha}^o$, in a Taylor series through the linear terms. The resulting approximation is then substituted into (5) to obtain

$$\sum_{i=1}^{n} w_i [y_i - f(x_i, \underset{\sim}{\alpha}^o) - \sum_{j=1}^{m} p_{ij}^o \delta_j^o]^2 , \tag{6}$$

where $p_{ij} = \partial f(x_i, \underset{\sim}{\alpha})/\partial \alpha_j$, m is the number of parameters in the model (m = 4 for model (1), m = 3 for model (4), and m = 2 if we required $\alpha_1 = \alpha_2$ and $\alpha_4 = 0$), and the superscript indicates that the partial derivatives are evaluated at $\underset{\sim}{\alpha} = \underset{\sim}{\alpha}^o$. Applying the LS principle to (6) we obtain the following system of m linear (in the unknown δ_j's) equations:

$$\sum_{i=1}^{n} w_i p_{ik}^o \sum_{j=1}^{m} p_{ij}^o \delta_j^o = \sum_{i=1}^{n} w_i p_{ik} [y_i - f(x_i, \underset{\sim}{\alpha}^o)] , \tag{7}$$

$$k = 1, \ldots, m.$$

Up to this point we have described the well known Gauss-Newton method for nonlinear least squares estimation. We now allow the weights to change on <u>each</u> iteration and rewrite (7) in matrix notation as follows:

$$\underset{\sim}{C}\underset{\sim}{\delta} = \underset{\sim}{G} ,$$

where
$$c_{jk} = \sum_{i=1}^{n} w_i p_{ij} p_{ik} , \qquad (8)$$

$$g_k = \sum_{i=1}^{n} w_i p_{ik} \left[y_i - f(x_i, \underset{\sim}{\alpha}) \right] ,$$

$$j,k = 1,\ldots,m.$$

The system of equations in (8) is solved for $\underset{\sim}{\delta}$ on each iteration until some convergence criteria has been satisfied. Each of the terms in $\underset{\sim}{C}$ and $\underset{\sim}{G}$ that depend on $\underset{\sim}{\alpha}$ (including the w_i's) are evaluated at the current value (i.e. the value obtained from the previous iteration). If on each iteration we define $w_i = 1$ $(i = 1,\ldots,n)$, then this IWLS procedure is equivalent to obtaining maximum likelihood estimates when the y_i's are assumed to be independent Gaussian random variables with constant variance. This is not a reasonable assumption for concentration-time curve data.

If we assume the y_i's are independent and follow a one parameter exponential distribution with mean $f(x_i, \underset{\sim}{\alpha})$, then Wedderburn (1974) has shown that the IWLS procedure with $w_i = 1/\text{var}(y_i)$ is the same as using the method of scoring to obtain maximum likelihood estimates. Charnes, Frome and Yu (1976) have shown that if the y_i's are nonnegative, and the log-likelihood is concave over the parameter space, then if the IWLS procedure converges to a stationary point of the likelihood equation it will be a global maximum of the likelihood function. These results require that $\text{var}(y_i) = V\left[E(y_i)\right]$ where V is a known function. In the next section we assume that the standard deviation of y_i is proportional

to $f(x_i,\underset{\sim}{\alpha})$. This is equivalent to assuming that the y_i's have a gamma distribution with expectation given by $f(x_i,\underset{\sim}{\alpha})$ and a "nusicance" parameter that does not depend on x. The less restrictive assumption of a know relationship between the mean and the variance leads to the maximum quasi-likelihood (MQL) estimates described by Wedderburn. Consequently, if we set $w_i = f(x_i,\underset{\sim}{\alpha})^{-2}$ in (8) and the IWLS procedure converges, the solution, $\hat{\underset{\sim}{\alpha}}$, will be a MQL estimate of $\underset{\sim}{\alpha}$ (see section 5).

In section 2 we stated that LAV estimates can be obtained using the IWLS procedure. This is done by using the estimates α^{k-1} obtained on the preceeding iteration to calculate residuals $r_i^k = y_i - f(x_i,\underset{\sim}{\alpha}^{k-1})$ which are then used to define weights for the k^{th} iteration

$$w_i = \begin{cases} |r_i^k|^{-1} & , \quad |r_i| > \varepsilon \\ 0 & \text{otherwise.} \end{cases}$$

It is possible for the algorithm to become unstable since the LAV estimates will usually interpolate at least two data values. When the algorithm does converge it sometimes proceeds at a very slow rate (compared to the constant weight least squares algorithm). A numerical example will be given in section 5.

Another robust procedure that has been proposed for linear regression is easily adapted to the nonlinear regression problem using IWLS. Let $\underset{\sim}{\alpha}^*$ denote the LAV estimate that has been obtained after k-1 iterations (or using NELMIN). Then on the k^{th} iteration calculate $r_i = y_i - f(x_i,\underset{\sim}{\alpha}^*)$, $i = 1,\ldots,n$, and determine $\underset{\sim}{s}$ = median $\{|r_i|\}$. Then following the robust procedure that has been proposed by Andrews (1974) for multiple linear regression, let $z_i = r_i/\underset{\sim}{s}$ and

$$w_i = \begin{cases} 1 & z_i = 0 \\ \dfrac{\sin(z_i/c)}{z_i/c} & |z_i| \leq c\Pi \\ 0 & |z_i| > c\Pi \end{cases}$$

The sine weights - which reduce the influence of large residuals depending on the value of c - are then used in (8) to obtain the correction vector $\underset{\sim}{\delta}$ and then the one step sine estimate

$$\hat{\alpha}_{sin1} = \hat{\underset{\sim}{\alpha}}^* + \underset{\sim}{\delta} \quad .$$

This procedure can then be iterated, and other weight functions can be used. Extensive Monte Carlo studies (see Andrew et al., 197) indicate that when a single location parameter is being estimated the one step sine estimate starting with the median (which is the LAV estimate) has good robustness properties. Welsh (1975) has discussed the extension of the one step sine estimate to the multiple linear regression problem. When the weight function is standardized to one at the origin estimates of the approximate parameter dispersion matrix are obtained by multiplying C^{-1} by

$$\frac{\Sigma_i w_i [y_i - f(x_i, \hat{\underset{\sim}{\alpha}})]^2}{\Sigma_i w_i - p} \quad .$$

In the results that follow, we shall use the LAV estimates as starting values, c = 1.5, and the IWLS procedure will be used. The resulting estimates will be refered to as SINE estimates.

5. MAXIMUM QUASI-LIKELIHOOD ESTIMATION

Suppose the y_i's are independent and that $\text{var}(y_i) \alpha f_i^2$, where f_i is $E(y_i)$ as defined by equation (1). The quasi-likelihood function $Q(y_i, f_i)$ for each observation is defined by the relation - see Wedderburn (1974) -

$$\frac{\partial Q(y_i, f_i)}{\partial f_i} = \frac{y_i - f_i}{f_i^2} \quad . \tag{9}$$

MQL estimates are obtained by solving the system of equations

$$\sum_{i=1}^{n} \frac{\partial Q(y_i, f_i)}{\partial \alpha_j} = \sum_{i=1}^{n} \frac{y_i - f_i}{f_i^2} p_{ij} = 0, \quad j=1,\ldots,4, \tag{10}$$

where $p_{ij} = \partial f(x_i, \underset{\sim}{\alpha})/\partial \alpha_j$. Since the MQL equations (10) are nonlinear in the unknown parameters, the method of scoring can be used to develop an algorithm to find a root of (10). This is done by expanding (10) in a first-order Taylor series about an initial estimate α^o

$$\Sigma_i f_i^{-2} p_{ij} (y_i - f_i) + \Sigma_i \Sigma_k \frac{\partial^2 Q(y_i, f_i)}{\partial \alpha_j \, \partial \alpha_k} \delta_k$$

and replacing the second partial derivatives with the negative of their expected values

$$-E\left(\frac{\partial^2 Q(y_i, f_i)}{\partial \alpha_j \, \partial \alpha_k}\right) = \frac{p_{ij} p_{ik}}{f_i^2}$$

This yields

$$\Sigma_i f_i^{-2} p_{ij} (y_i - f_i) - \Sigma_i f_i^{-2} p_{ik} \Sigma_j p_{ij} \delta_j = 0$$

$$j = 1,\ldots,4,$$

where the f_i's and p_{ij} are evaluated at the $\alpha = \alpha^o$. This is the same system of equations

$$\underset{\sim}{C}\underset{\sim}{\delta} = \underset{\sim}{G}$$

that was obtained in section 3 with $w_i = f_i^{-2}$. Consequently, the MQL estimates can be obtained using the IWLS procedure. Wedderburn (1974) has shown that when the constant of proportionality in the mean-variance relationship -- $\text{var}(y_i) = \Phi f_i^{-2}$ -- is known to be one, then the elements of the inverse of the approximate dispersion matrix of the MQL estimates are given by

$$E\left(\frac{\partial Q}{\partial \alpha_j}\frac{\partial Q}{\partial \alpha_k}\right), \quad j,k = 1,\ldots,4.$$

The dispersion matrix of the MQL estimates is estimated by obtaining the inverse of the matric C evaluated at the MQL estimate, which is then scaled by the factor

$$\hat{\Phi} = \frac{1}{n-4}\Sigma_i\left[\frac{y_i - f(x_i,\hat{\underset{\sim}{\alpha}})}{f(x_i,\hat{\underset{\sim}{\alpha}})}\right]^2$$

Note that the MQL estimate is a solution of the system of equations (10), and does not provide a minimum of the weighted sum of squares (5). A check on the solution is obtained by evaluating (10) at the MQL estimate $\hat{\underset{\sim}{\alpha}}$.

6. COMPUTATIONAL RESULTS

In the previous sections we have shown how IWLS can be used to obtain LAV, LS, MQL and robust estimates using SINE weights. The MQL estimates are obtained under the assumption that the standard deviation of y is proportional to the E(y) for fixed x. Clearly, other possible weight functions are possible for the MQL and robust estimation procedures. The possibilities that we have presented are attempts to deal with the obvious inadequacies of the constant variance assumption of the usual (constant weight) LS analysis. If the data is otherwise "good" (i.e. no outliers) the MQL procedure or some variation (i.e. assume variance of y is proportional to its expectation) should produce a reasonable estimation procedure. Specification of the mean variance relationship is based on experience with similar data and knowledge of the error structure, which depends on both assay and subject variation. In many practical situations the one-compartment model represents a first approximation and departures from this theoretical model as well as possible aberrant data values indicate that a robust estimation procedure should be considered. It is important to emphasize that the estimation procedure is often applied to a number of concentration-time curves that are obtained in a comparative bioavailability study, and that the estimation procedure should be the same for each curve.

We now consider two numerical examples using data obtained during a bioavailability study of hydroflumethiazide, a diuretic and antihypertensive agent. In this study, volunteer subjects were hydrated and then administered a 100 mg dose (2 x 50 mg tablets) of hydroflumethiazide. Plasma samples were obtained from each subject at predetermined times and assayed for

hydroflumethiazide by a sensitive fluorescence technique developed by Smith, Smith and Yakatan (1976). Each of the estimation procedures (LAV, LS, MQL and SINE) was then applied to the concentration-time curve data and results are presented in summary form. The computational procedure is briefly summarized as follows:

1. [Initial Estimate.] Starting with a guess use subroutine NELMIN to obtain starting values, using either LP = 1 (LS) or LP = 2 (LAV).
2. [Specify Weight Function.] Define the weight function that will be used on each iteration.
3. [Linear System of Equations.] Calculate $\underset{\sim}{C}$ and $\underset{\sim}{G}$ as defined in (8) using the current value of $\underset{\sim}{\alpha}$.
4. [Solve for Correction Vector.] Solve $\underset{\sim}{C}\,\underset{\sim}{\delta} = \underset{\sim}{G}$ for the correction vector $\underset{\sim}{\delta}$.
5. [Continue ? .] Check for convergence. If the convergence criteria have not been satisfied set $\underset{\sim}{\alpha} \leftarrow \underset{\sim}{\alpha} + \underset{\sim}{\delta}$. If maximum number of iterations has not been reached then go to Step 3. For convergence we require the $|\delta_j| < \varepsilon(|\alpha_j| + \eta)$, $j = 1,\ldots,m$, where ε, η are small positive constants such that $\varepsilon \cdot \eta$ is greater than the precision of the computer that is used.

All computations were done on a CDC 66-6400 (precision $\approx 10^{-14}$) using a FORTRAN program written by one of the authors. The IWLS procedure was terminated when the relative change in each parameter was less than 10^{-6}.

The data for the first example is given in the first two columns of *Exhibit 8. In this example* we assume that the delay time is equal to zero. The initial guesses were $\alpha_1^o = 1$, $\alpha_2^o = .5$ and $\alpha_3^o = 1000$. NELMIN was then

used (as described in Section 2) to obtain the LS and LAV estimates (see Exhibit 9). In both cases local minima were achieved and the IWLS procedure terminated after one iteration. Estimates of the approximate parameter dispersion/correlation matrix for the LS estimates are

$$s^2 \underset{\sim}{C}^{-1} \begin{bmatrix} 9.35 \times 10^{-2} & -.9211 & -.962 \\ -2.69 \times 10^{-2} & 9.10 \times 10^{-3} & .969 \\ -53.79 & 16.9 & 3.34 \times 10^{4} \end{bmatrix},$$

where $\underset{\sim}{C}$ - see (8) - is evaluated at the LS estimate and $s^2 = \Sigma_i |y_i - f(x_i, \hat{\alpha}_{LS})|^2/(n-3) = 1855$. The fitted values and residuals are shown in Exhibit 8.

The MQL estimates were obtained (after 12 iterations) using the IWLS procedure with the LAV estimates as starting values. The MQL estimates are given in Exhibit 9, and the estimated approximate dispersion/correlation matrix (see section 5) is

$$\hat{\Phi}\, \underset{\sim}{C}^{-1} = \begin{bmatrix} .117 & -.610 & -.651 \\ -.276 \times 10^{-3} & 1.75 \times 10^{-4} & .791 \\ -10.2 & .478 & 2090 \end{bmatrix},$$

where $\hat{\Phi} = .05204$. The fitted values and residuals are given in Exhibits 8 and 9.

The SINE estimates (see Exhibit 9) were obtained with c = 1.5 using the LAV estimates as starting values and 30 iterations were required. The estimated approximate dispersion/correlation matrix is obtained by multiplying $\underset{\sim}{C}^{-1}$ by $\Sigma_i w_i |y_i - f(x_i, \alpha_{SINE})|^2/|\Sigma_i w_i - 3| = 1224.8$ and is

$$\begin{bmatrix} 6.88 \times 10^{-2} & -.884 & -.940 \\ -1.47 \times 10^{-2} & 4.03 \times 10^{-3} & .950 \\ -30.6 & 7.48 & 1.54 \times 10^{4} \end{bmatrix}.$$

The fitted values, residuals and the weights used on the last iteration are given in the last three columns of Exhibit 8.

The concentration-time curve data for the second example is shown in columns 1 and 2 of Exhibit 10. To illustrate the importance of the delay time parameter (α_4), the LS estimates were obtained first with $\alpha_4 = 0$. For this restricted fit we obtained $\alpha_1 = .684$, $\alpha_2 = .196$, $\alpha_3 = 286$ and the minimum sum of squares is 6354. The LS estimates for the four parameter model are $\alpha_1 = 1.60$, $\alpha_2 = .156$, $\alpha_3 = 235$, $\alpha_4 = .440$ and the minimum sum of squares is 1751. The fitted values and residuals are given in Exhibit 10, and estimates of the parameters and their standard deviations are listed in Exhibit 11. The fitted curves for both the three parameter and four parameter model are plotted in Exhibit 12.

The LAV estimates (see Exhibit 11) were obtained using NELMIN with initial guesses of $\alpha_1 = 1.0$, $\alpha_2 = .5$, $\alpha_3 = 1000$ and $\alpha_4 = .3$. This required 3113 function evaluations. The IWLS procedure terminated after one iteration. The LAV estimates were used as starting values for the SINE estimates which are given in Exhibit 11. The LS estimates were obtained from NELMIN after 301 function evaluations, and were used as initial estimates in the MQL estimation procedure (see Exhibits 10 and 11 for results). The fitted curves for the MQL and SINE procedures are plotted with the data in Exhibit 13.

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Exhibit 1. One-compartment Open Model with First-order Absorption and Elimination

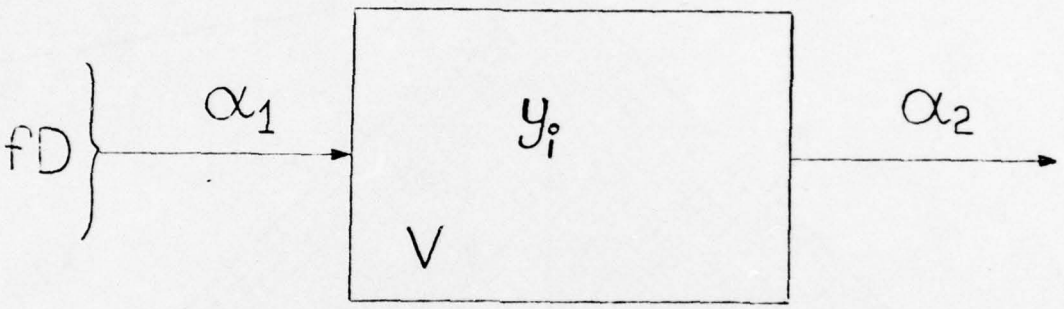


Exhibit 2. Three Dimensional Perspective View of Sum of Squares Surface

$\phi = 8.1°$ $\theta = 45°$

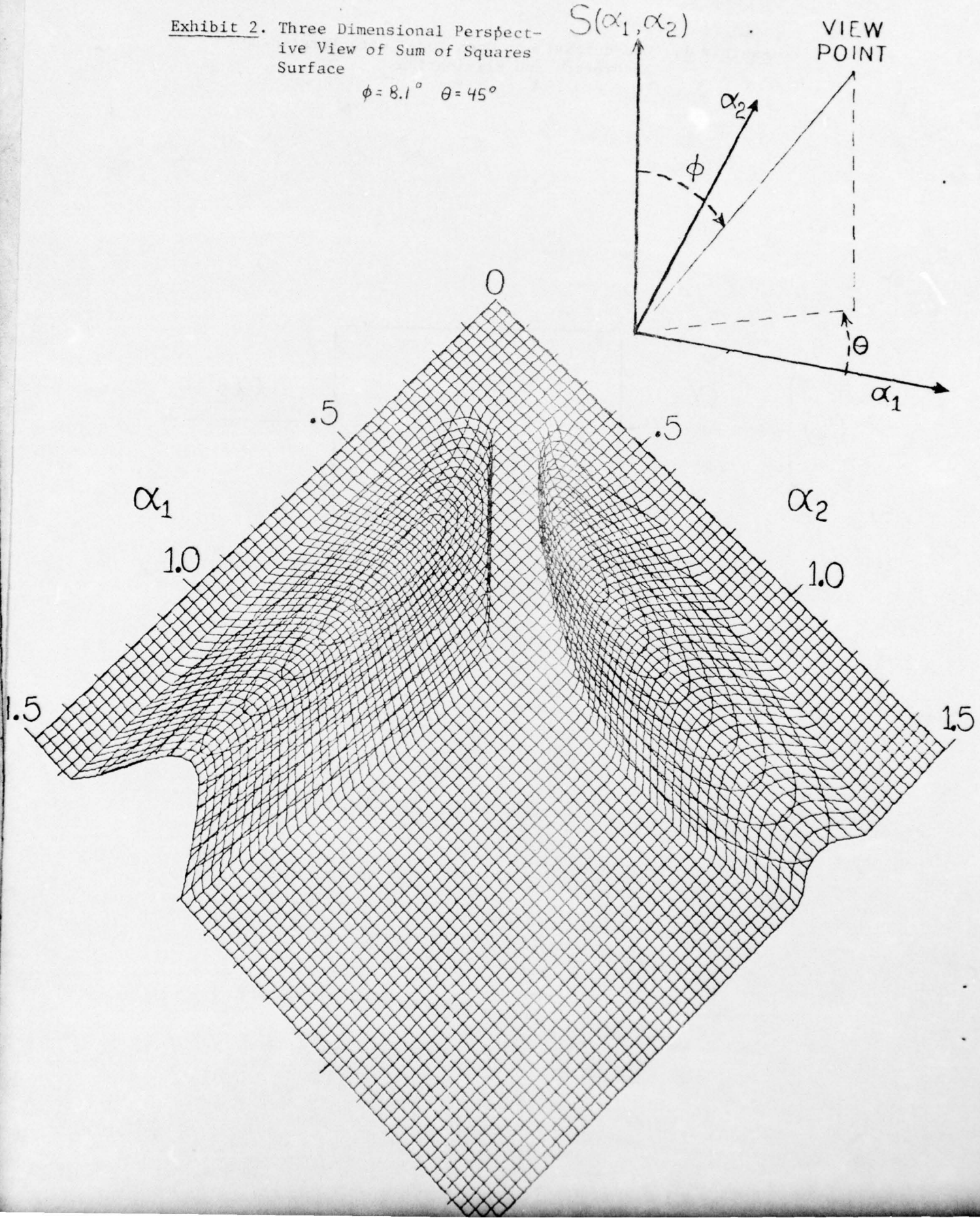


Exhibit 3. Three Dimensional Perspective View of Sum of Squares Surface

$\phi = 8.9°$ $\theta = 19°$

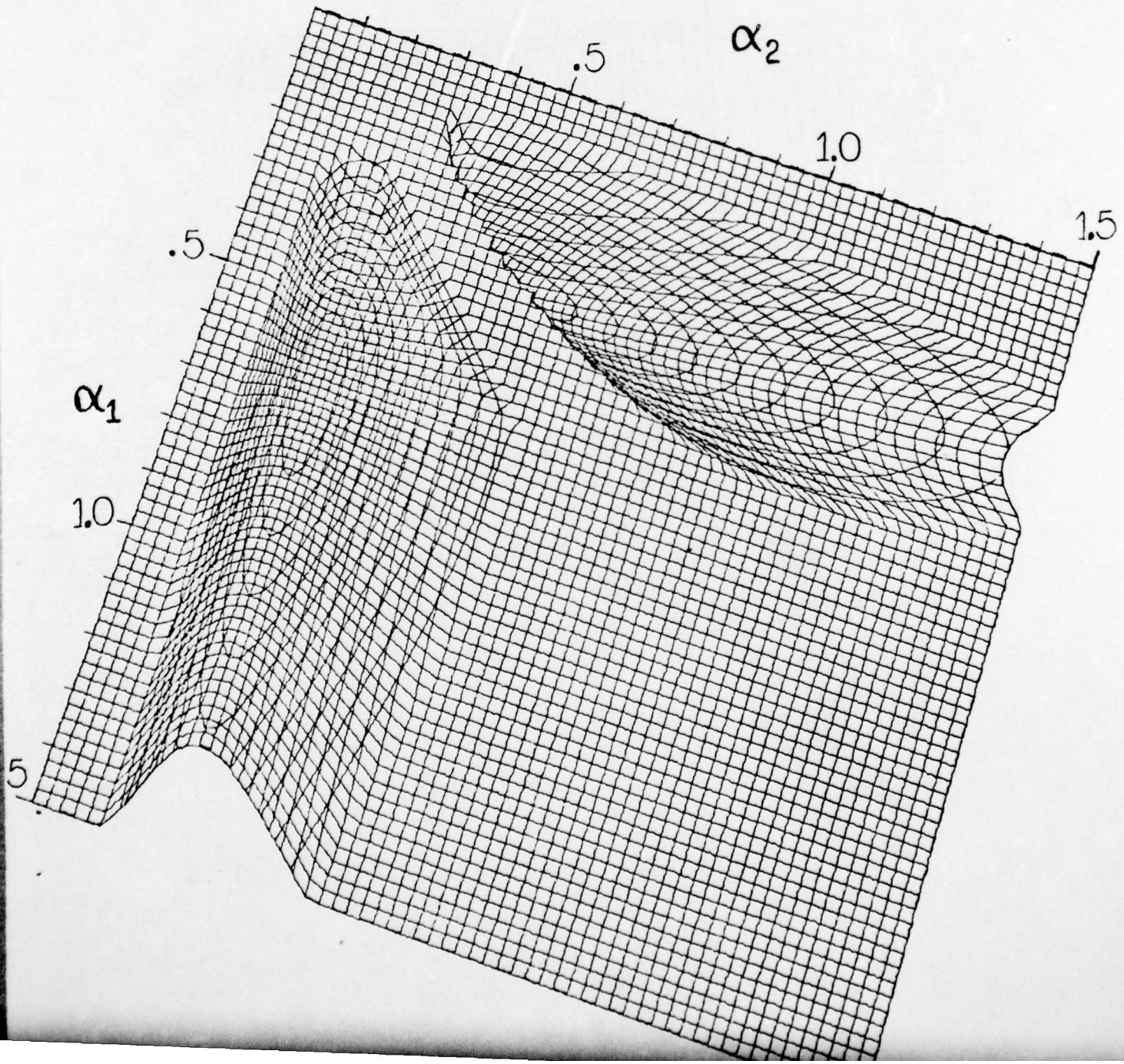


Exhibit 4. Three Dimensional Perspective View of Sum of Squares Surface

$\phi = 45°$ $\theta = 4.2°$

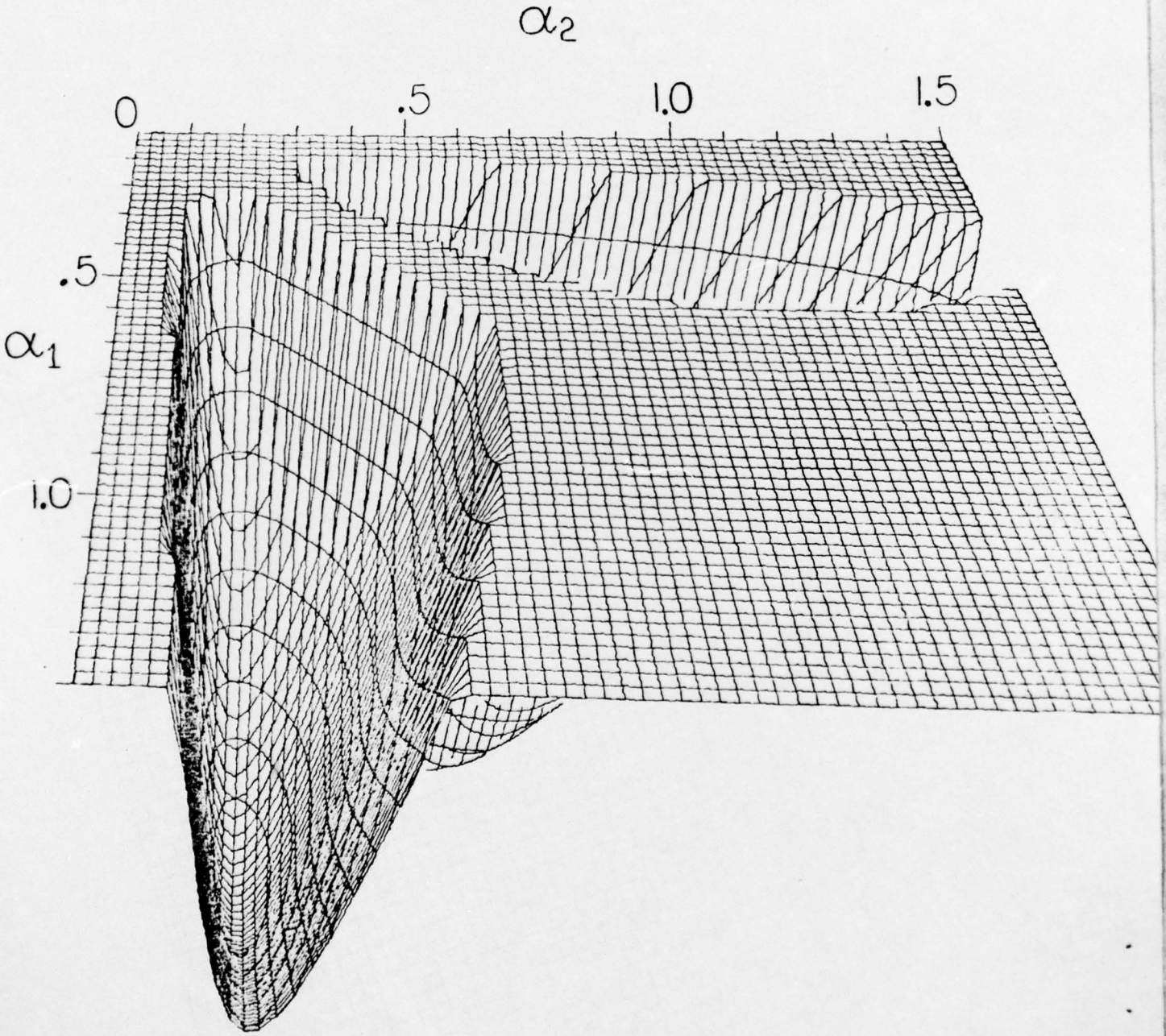


EXHIBIT 5

```
      FUNCTION FN(J)
      COMMON N,NP,LP,X(300),Y(300)
C
C        FUNCTION REQUIRED BUY SUBROUTINE NELMIN TO FIT THE ONE
C                  COMPARTMENT OPEN MODEL
C              LP EQUALS ONE FOR LEAST ABSOLUTE VALUE FIT
C              LP EQUALS TWO FOR THE LEAST SQUARES FIT
C        NP IS THE NUMBER OF PARAMETERS ( EITHER 3 OR 4 )
C        N IS THE NUMBER OF DATA VALUES
C        X(I) DENOTES THE TIME AT WHICH THE ITH CONCENTRATION IS
C                OBTAINED,
C        Y(I)  IS THE OBSERVE CONCENTRATION AT TIME X(I)
C
      DIMENSION A(4)
      FE2(I)=C*(EXP(-A(2)*(X(I)-A(4)))-EXP(-A(1)*(X(I)-A(4))))
      DATA BIG/1.E20/,EPS/0.00001/
      FN= 0.0
         IF(NP.LT.4) A(4)= 0.0
         IF(A(4).LT.0.0) FN= BIG
         IF( (A(1)-A(2)).LE.EPS ) FN= BIG
         IF( FN.GT.0.0 ) RETURN
      C= A(3)*A(1)/ ( A(1)-A(2) )
         IF( LP.EQ.2 ) GO TO 150
      DO 100 I= 1,N
  100 FN= FN + ABS( Y(I)-FE2(I) )
         RETURN
  150 DO 200 I= 1,N
  200 FN= FN + ( Y(I)- FE2(I) )**2
         RETURN
         END
```

Exhibit 6 Outlier Patterns

Time (hours)	Truth (y_i)	Pattern Number 1	2	3	4	5	6	7
.083	10.9	10.9	10.9	10.9	10.9	10.9	10.9	10.9
.167	19.1	19.1	19.1	19.1	19.1	19.1	19.1	19.1
.250	25.3	25.3	25.3	25.3	25.3	25.3	25.3	25.3
.500	35.4	15.0+	15.0+	15.0+	55.0+	55.0+	55.0+	35.4
.750	38.5	38.5	20.0+	20.0+	38.5	60.0+	60.0+	38.5
1.00	38.4	38.4	38.4	20.0+	38.4	38.4	60.0+	38.4
1.50	34.8	34.8	34.8	34.8	34.8	34.8	34.8	34.8
2.25	28.2	28.2	28.2	28.2	28.2	28.2	28.2	28.2
3.00	22.6	22.6	22.6	22.6	22.6	22.6	22.6	22.6
4.00	16.7	16.7	16.7	16.7	16.7	16.7	16.7	16.7
6.00	9.2	9.2	9.2	9.2	9.2	9.2	9.2	9.2
8.00	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
10.0	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
12.0	1.5	1.5	1.5	1.5	1.5	1.5	1.5	15.0+

+ Aberrant value.

Exhibit 7. LS and LAV Estimates of Pharmacokinetic and Bioavailability Parameters for Outlier Patterns.

		Pattern Number							
		0	1	2	3	4	5	6	7
α_1	LS	2.99	2.14	1.85	5.27	3.43	2.95	2.27	3.33
	LAV	2.99	2.99	2.99	3.03	3.00	3.00	2.98	2.99
α_2	LS	.300	.306	.287	.163	.328	.409	.525	.257
	LAV	.301	.301	.301	.298	.301	.301	.302	.300
α_3	LS	50.0	49.5	45.7	29.2	54.3	65.8	83.4	47.0
	LAV	50.0	50.0	50.0	49.5	50.0	50.0	50.2	50.0
t*	LS	.854	1.06	1.19	.681	.757	.778	.840	.833
	LAV	.854	.854	.854	.850	.853	.853	.855	.854
f*	LS	38.7	35.8	32.4	26.1	42.4	47.9	53.7	37.9
	LAV	38.7	38.7	38.7	38.5	38.7	38.7	38.8	38.7
AUC	LS	167.	162.	159.	179.	166.	161.	159.	183.
	LAV	166.	166.	166.	166.	166.	166.	166.	167.
O.F.+	LS	.007	305.	415.	434.	289.	468.	440.	172.
	LAV	.245	20.6	39.1	59.3	19.8	41.3	62.8	13.7
F.E.+	LS	178.	193.	187.	314.	232.	188.		183.
	LAV	256.	308.	322.	270.	258.	264.	305.	311.

+ O.F. = value of the objective function; F.E. = number of function evaluations performed by NELMIN.

Exhibit 8. Concentration-time Curve Data, Fitted Values and Residuals for Example 1.

		LS		LAV		MQL		SINE		
x_i (hours)	y_i (ng/ml)	$\hat{y}_i$	r_i	$\hat{y}_i$	r_i	$\hat{y}_i$	r_i	$\hat{y}_i$	r_i	w_i
0.5	169	154	15	169	0	168	1	148	21	.922
1.0	199	248	-49	265	-66	252	-53	238	-39	.755
1.5	258	300	-42	315	-56	288	-30	289	-31	.843
2.0	364	324	40	335	29	299	65	313	51	.597
2.5	398	330	68	337	61	296	102	319	79	.216
3.0	328	323	5	328	0	286	42	315	13	.969
4.0	267	291	-24	294	-28	257	10	286	-20	.933
6.0	141	206	-65	217	-76	199	-58	211	-70	.336
8.0	161	135	26	153	8	151	10	146	15	.959
10.0	107	86	21	107	0	115	-8	99	8	.987
12.0	60	55	5	75	-14	88	-28	66	-6	.993
24.0	20	3	17	9	11	17	3	6	14	.965

Exhibit 9. Estimates for Exhibit 8 Data.

Pharmacokinetic Parameters	LS	LAV	MQL	SINE
α_1	.656	.848	1.16	.697
α_2	.234	.181	.137	.202
α_3	584.	513.	398.	529.
Bioavailability Parameters				
t*	2.44	2.32	2.10	2.50
c*	330.	338.	299.	319.
AUC	2501.	2841.	2916.	2626.

Exhibit 10. Concentration-time Curve Data, Fitted Values and Residuals for Example 2.

		LAV		LS		MQL		SINE		
x_i (hours)	y_i (ng/ml)	y_i	r_i	y_i	r_i	y_i	r_i	y_i	r_i	w_i
0.50	26	26	0	22	5	26	0.1	26	0	1.000
1.00	117	133	-16	133	-16	130	-13	133	-16	0.0
1.53	177	177	0	175	2	170	7	177	-0.1	.996
2.00	206	188	18	183	23	179	27	188	18	0.0
2.50	186	186	0.2	179	7	177	9	186	0.1	.982
3.00	166	178	-12	171	-5	169	-3	178	-12	0.0
4.00	120	156	-36	149	-29	149	-29	156	-36	0.0
6.00	115	115	0	109	6	111	4	115	-0.1	.985
8.00	84	84	-0.1	80	4	82	2	84	-0.2	.928
10.0	62	62	0.5	59	3	61	1	62	0.4	.771
12.0	45	45	0	43	2	45	-0.3	45	0	.998

Exhibit 11. Results for Example 2.

Pharmacokinetic Parameters	LAV	LS	MQL	SINE
α_1	1.46	1.60	1.54	1.46
s.d.	---	.433	.338	.012
α_2	.156	.156	.149	.156
s.d.	---	.026	.013	6.07×10^{-4}
α_3	246.	235.	231.	246.
s.d.	---	20.4	16.8	.660
α_4	.423	.440	.422	.423
s.d.	---	.052	.017	1.04×10^{-3}
SSW	82.8	1751.	.075	.201
Iterations	1	1	5	5
Bioavailability Parameters				
t*	2.14	2.05	2.10	2.14
f*	188.	183.	180.	188.
AUC	1572.	1506.	1545.	1573.

Exhibit 12. LS Fits for Example 2 With $\alpha_4 = 0$ and With α_4 Estimated From the Data.

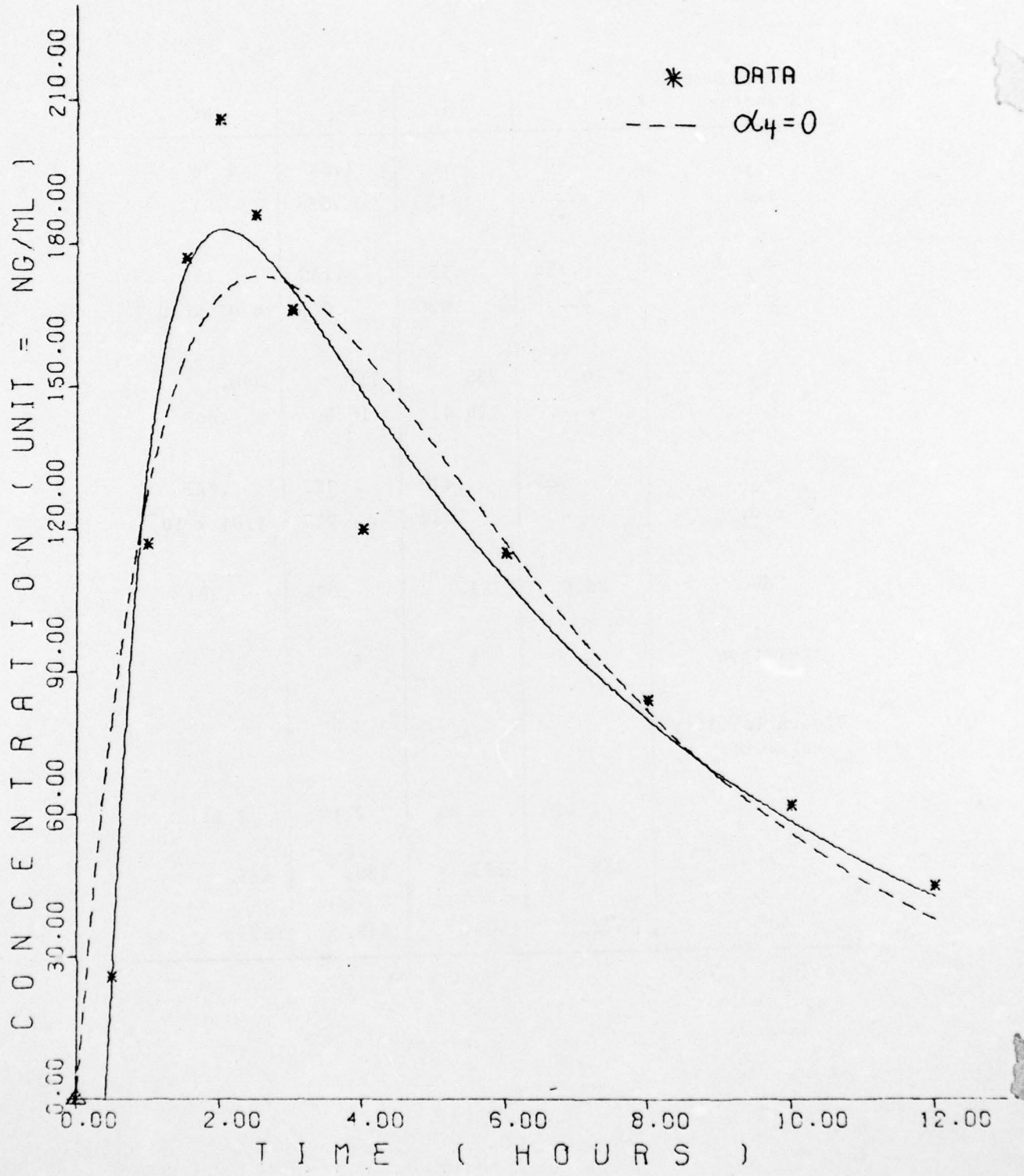
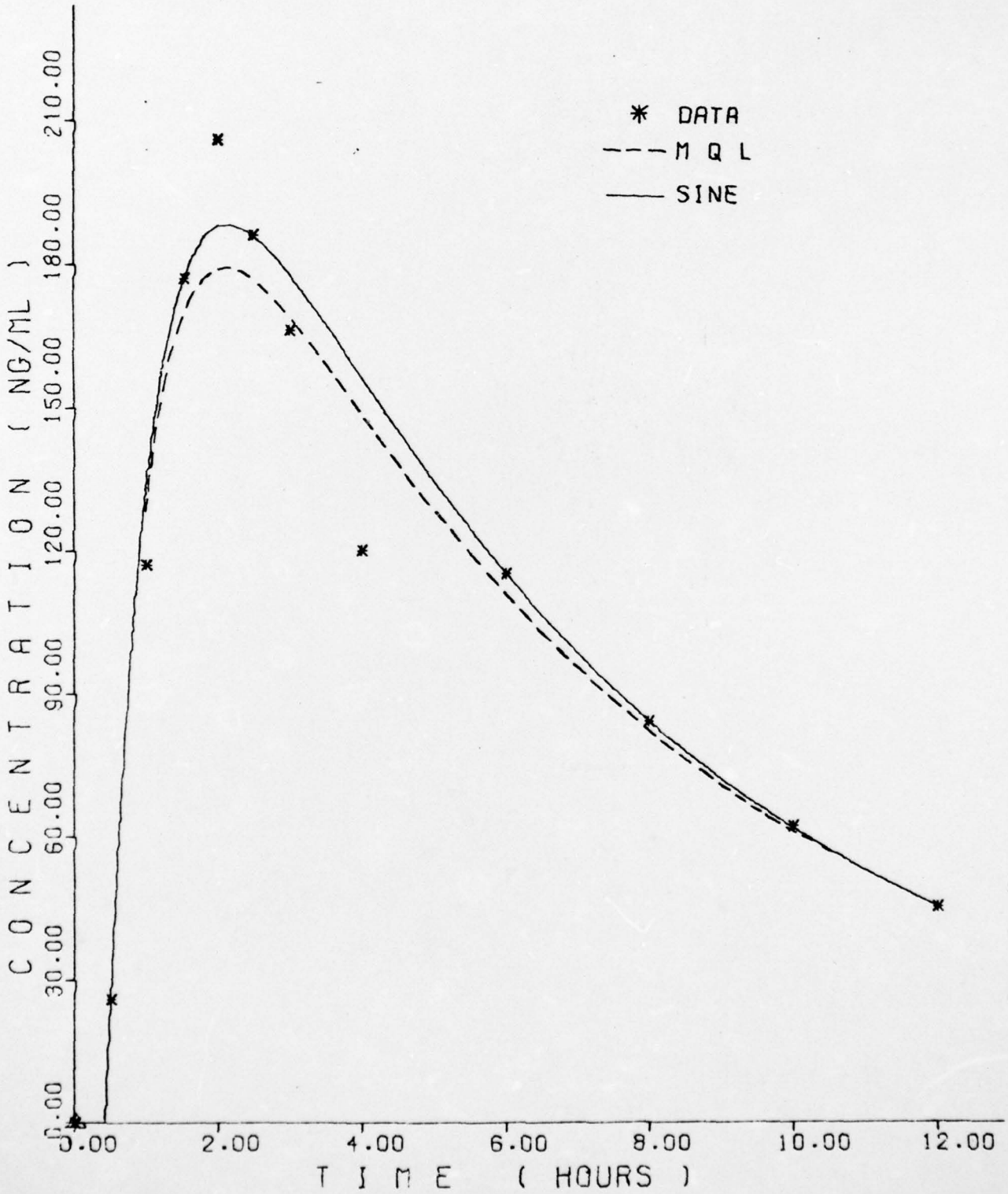


Exhibit 13. MQL and SINE Fits for Example 2.



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13. ABSTRACT

A comparative blood-level trial is undertaken to evaluate the in vivo performance of drug formulations in human subjects. A known amount of drug is administered and plasma levels are measured at specified times. The resulting concentration-time curve reflects the absorption, distribution and elimination of the drug. The simplest model that represents this kind of data is the one compartment open model. In many situations this serves as a convenient model for estimating the bioavailability parameters--area under the concentration-time curve, time to peak concentration, and peak concentration.

The one compartment open model is nonlinear in the unknown parameters and is usually fit using least squares. Gradient methods often fail for real world data, and ~~we have found~~ the Nelder-Mead simplex algorithm provides a useful alternative. Further, ~~we propose that~~ least absolute deviation criteria can be used as an ~~robust~~ alternative to least squares. Both least absolute deviation and least squares can be obtained using an iterative weighted least squares algorithm. The iterative weighted least squares procedure is also used to obtain maximum quasi-likelihood estimates and robust estimates using the sine weight function. Two numerical examples are presented.

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Bioavailability						